REMARKS/ARGUMENTS

Reconsideration and withdrawal of the rejections of the present application are respectfully requested in view of the amendments to the claims and remarks presented herewith, which place the application into condition for allowance.

Status of the Claims and Formal Matters

Claims 40-42, 43, 71 and 78-81 are currently pending in this application. In order to advance prosecution and to overcome rejections, claim 40 had been amended to clarify the instant method of detecting protein expression and folding. Claim 71 has been amended to depend from claim 40 and claims 41, 42 and 44 have been amended to clarify the claimed subject matter.

New claims 78-81 have been added. The support for the new claims is found at pages 8, 9 and in Figures 1-9 of the WO 2004/046730. No new matter has been added.

Rejections under §112, 1st paragraph

35 U.S.C. §112, First Paragraph - Written Description.

Claims 40-42, 44 and 71 were rejected under 35 U.S.C. §112, 1st paragraph as allegedly failing to comply with the written description requirement. Amendments to claim 40, clarifying the instant method of detecting expression and correct folding of a protein of interest with the use of a *ble* marker protein, renders the rejection moot.

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1111, 1117 (Fed. Cir. 1991). Stated otherwise, the test for sufficiency of support in an application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later-filed subject matter. *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985). Such a test is conducted from the standpoint of one of skill in the art at the time the application was filed. *Wang Labs v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993). Consequently, based on the knowledge of those skilled in the art at the time of filing,

together with the disclosure provided in the instant specification, Applicants respectfully submit that amended claims 40, the dependent claims 41, 42, 44, 71 and new claims 78-81 satisfy the written description requirement under §112, 1st paragraph. Reconsideration and withdrawal of the §112, 1st paragraph rejection for an alleged failure to comply with the written description requirement is respectfully requested.

Rejections under § 112, second paragraph.

Claims 40-42 and 44 were rejected under 35 U.S.C. §112, 2nd paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In view of the amendments to claim 40, Applicants urge that this rejection is moot and should be withdrawn.

Rejections under §102(a)

Claims 40-42 and 44 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Gautier et al., 1996, Experimental Cell Research 224, 291-301, "Gautier". The Office Action contends that Gautier allegedly discloses fusion genes carrying Drosophila alcohol dehydrogenase (Dro-ADH) fused to Sh ble, expressed in mammalian cells and thus anticipates the instant claims. This rejection is respectfully traversed in view of the claim amendments and remarks presented herewith.

Gautier relates to small fusion genes carrying phleomycin resistance and Drosophila alcohol dehydrogenase reporter properties and their subsequent application in retroviral vectors. Specifically, Gautier teaches sh ble fusions and uses them to confer resistance and reporter activity in the same polypeptide. The retroviral vectors in Gautier were inoculated in the E3 chick embryo and cells from different organs were later stained for ADH activity. However, Gautire does not teach or suggest a method of detecting a protein expression and folding comprising fusing said protein to a ble marker protein wherein the ble fusion protein must adopt the correct conformation to bind an antibiotic in order to demonstrate the correctly folded nature of the ble fusion protein;and wherein detection of antibiotic binding of the ble fusion is determined using a labeled or unlabeled antibiotic. Under §102, a reference can only be anticipatory if it enables that which it is alleged to anticipate. *Elan Pharmaceuticals v. Mayo Foundation for Medical Education and Research* 346 F.3d 1051, 68 U.S.P.Q.2d 1373, (Fed. Cir. 2003). Gautier also fails to teach or disclose all of the claim limitations, namely the recitation of

a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Consequently, Applicants assert that a §102(b) rejection in view of Gautire is moot. Reconsideration and withdrawal of the rejection is hereby respectfully requested.

Claims 40-42 and 44 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Bennett et al., (1998 Bio Techniques 24(30): 478-482), "Bennett". The Office Action contends that Bennett allegedly teaches a ble fusion protein comprising green fluorescent protein (GFP) and Zeocin™-resistance gene Sh ble that can be allegedly used for visual screening and selection of transfected mammalian cells. This rejection is respectfully traversed in view of the claim amendments and remarks presented herewith.

Bennett relates to fusions to generate a bifunctional protein for the identification and selection of transfected mammalian cells. This bifunctional protein was aimed to determine transient transfection efficiencies in tissue culture cells using fluorescence microscopy carrying phleomycin resistance and Drosophila alcohol dehydrogenase reporter properties and their subsequent application in retroviral vectors. However, Bennett does not teach or suggest a method of detecting a protein expression and folding comprising fusing said protein to a ble marker protein wherein the ble fusion protein must adopt the correct conformation to bind an antibiotic in order to demonstrate the correctly folded nature of the ble fusion protein; and wherein detection of antibiotic binding of the ble fusion is determined using a labeled or unlabeled antibiotic.

Under §102, a reference can only be anticipatory if it enables that which it is alleged to anticipate. *Elan Pharmaceuticals v. Mayo Foundation for Medical Education and Research* 346 F.3d 1051, 68 U.S.P.Q.2d 1373, (Fed. Cir. 2003). Bennett also fails to teach or disclose all of the claim limitations, namely the recitation of a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir.1987). Consequently, Applicants assert that a §102(b) rejection in view of Bennett is moot. Reconsideration and withdrawal of the rejection is hereby respectfully requested.

Claims 40-42 and 44 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Baron et al., Gene, 1992, 15; 114(2):239-243, "Baron". The Office Action contends that Baron allegedly discloses She ble gene fused with E.coli lac Z in order to generate bifunctional β-galactosidase:phleomycin-resistance fusion protein as a potential marker for eukaryotic cells. This rejection is respectfully traversed in view of the claim amendments and remarks presented herewith.

Baron demonstrates the bifunctionality of She ble fusion 130 Kda hybrid protein in E.coli and in the fungus and Tolypocladium geodes. The Baron system appears to be a potentially useful tool for the direct selection of transformants in a wide variety of prokaryotic and eukaryotic hosts. However, Barron does not teach or suggest a method of detecting a protein expression and folding comprising fusing said protein to a ble marker protein wherein the ble fusion protein must adopt the correct conformation to bind an antibiotic in order to demonstrate the correctly folded nature of the ble fusion protein; and wherein detection of antibiotic binding of the ble fusion is determined using a labeled or unlabeled antibiotic

Under §102, a reference can only be anticipatory if it enables that which it is alleged to anticipate. *Elan Pharmaceuticals v. Mayo Foundation for Medical Education and Research* 346 F.3d 1051, 68 U.S.P.Q.2d 1373, (Fed. Cir. 2003). Barron also fails to teach or disclose all of the claim limitations, namely the recitation of a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Consequently, Applicants assert that a §102(b) rejection in view of Barron is moot. Reconsideration and withdrawal of the rejection is hereby respectfully requested.

Rejections under §103(a)

Claims 42 and 43 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Blackburn et al. (WO 0227327), "Blackburn"in view of Bennett. The Office Action contends that it would have been obvious to the skilled artisan to create "tagged" ble fusion proteins by substituting a hexa-histidine tag disclosed by Blackburn for the GFP reporter protein disclosed by Bennett and purify the protein by Zeocin selection. The Applicants respectfully traverse this rejection.

Blackburn relates to methods of producing proteins in which one or more domains are full length and correctly folded and which are each tagged at either the N or C-terminus with one or more marker moieties and arrays containing such proteins. Blackburn does not teach or suggest a method of detecting a protein expression and folding comprising fusing said protein to a ble marker protein wherein the ble fusion protein must adopt the correct conformation to bind an antibiotic in order to demonstrate the correctly folded nature of the ble fusion protein; and wherein detection of antibiotic binding of the ble fusion is determined using a labeled or unlabeled antibiotic

Bennett does not remedy the deficiencies of Blackburn. As discussed above, Bennett relates to fusions to generate a bifunctional protein for the identification and selection of transfected mammalian cells. This bifunctional protein was aimed to determine transient transfection efficiencies in tissue culture cells using fluorescence microscopy carrying phleomycin resistance and Drosophila alcohol dehydrogenase reporter properties and their subsequent application in retroviral vectors. However, nothing in Bennett would cause the ordinary scientist to extrapolate the capture and/or binding of She ble fusion protein via the She ble antibiotic binding pocket. Furthermore, Bennett is silent with regard to the She ble unusual property of stoichiometric antibiotic resistance wherein the mechanism of action is antibiotic binding rather than catalytic breakdown of the antibiotic.

As detailed above, Blackburn does not teach or suggest all the elements of the instant claims. Bennet does not cure the deficiencies of Blackburn. Specifically, Bennet does not teach or suggest a method of detecting a protein expression and folding comprising fusing said protein to a ble marker protein wherein the ble fusion protein must adopt the correct conformation to bind an antibiotic in order to demonstrate the correctly folded nature of the ble fusion protein;and wherein detection of antibiotic binding of the ble fusion is determined using a labeled or unlabeled antibiotic.

Prior art is not limited just to the references being applied, but includes the understanding of one of ordinary skill in the art. The prior art reference (or references when combined) need not teach or suggest all the claim limitations, however, Office personnel must explain why the

difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art.[1]

Accordingly, since combination of the references would fail to teach or suggest every element of the claims, the Examiner must explain why the differences between the teachings of the prior art and the claimed invention. Withdrawal of the obviousness rejection is respectfully requested.

CONCLUSION

Favorable action on the merits is respectfully requested. If any discussion regarding this Response is desired, the Examiner is respectfully urged to contact the undersigned at the number given below, and is assured of full cooperation in progressing the application to allowance.

Applicants believe no additional fees are due with the filing of this Response. However, if any additional fees are required or if any funds are due, the USPTO is authorized to charge or credit Deposit Account Number: **50-0311**, Customer Number: **35437**, Reference Number: **27353-513 US1**.

Respectfully submitted,

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[1] MPEP § 2141